REMARKS

On behalf of the Applicants, the undersigned wishes to express appreciation to Examiner Sharareh and his supervisor, Dr. Russell Travers, for the telephonic interview granted on October 7, 2003. This interview was extremely helpful in agreeing on claim language that would address the concerns of the Examiner and his Supervisor, as well as the Applicants.

Claims 2-26, 34, 36-38, 68 and 69 will remain in the application, after entry of this amendment.

Claims 1, 35 and 39-67 are being canceled, without prejudice, by this amendment.

New Claim 68 replaces Claim 1 and new Claim 69 replaces Claim 35.

New Claim 68 is the claim suggested by Examiner Sharareh to replace Claim 1 to overcome some 35 USC 112, second paragraph, concerns that he and his Supervisor had. This claim, with a few minor revisions to correct typos, is acceptable to Applicants. New Claim 68 recites all of the limitations of canceled Claim 1 but in a different format. It has been agreed that the limitation of Claim 1 obviated the rejections under 35 USC 102(b) as being anticipated by either U.S. Patent 4 844 907 (Elger et al) or U.S. Patent 6 238 695 (Makooi-Morehead et al). Hence, new Claim 68 obviates the 35 USC 102(b) rejection also.

In the note that accompanied the suggested generic claim, the Examiner noted that "the language and argument regarding the new claim must overcome the 103 rejection as well". However, the undersigned was unaware that the 35 USC 103 rejection was still an issue because it was not discussed during the telephonic interview on October 7, 2003 and has been discussed during the telephonic interview between the Examiner, the undersigned and the Applicants on May 1, 2003. The rejection is also addressed in the paragraph bridging pages 20 and 21 of Applicants' Response of July 8, 2003.

Nevertheless, the response to the 35 USC 103 rejection will be amplified below.

The claims are patentable over the combination of references applied because the combination of references does not establish a prima facie case of obviousness.

The establishment of a prima facie case of obviousness requires (1) some suggestion or motivation to modify or combine references, (2) a reasonable expectation of success and (3) that the combination of references teach or suggest all the claim limitations. The combination of references applied by the Examiner does not provide evidence that meets the criteria of a prima facie case for the following reasons:

U.S. PATENT 4 844 907 (Elger et al)
IN VIEW OF U.S. PATENT 6 238 695 (Makooi-Morehead et al)

The tablet composition of claim 1 requires the presence of

a) a rapidly precititating drug as the sole active pharmaceutical ingredient in an amount of about 5 to about 60%;

b) a polymeric binder in an amount of about 2 to about 60%;

c) a superdisintegrant in an amount of about 6 to about 40%; and

d) a lubricant in an amount up to about 5%.

The Elger et al patent describes a tablet that requires the presence of two active pharmaceutical ingredients, namely a narcotic analgesic and a non-steroidal anti-inflammatory. Elger et al also specifically teaches that they exclude lubricants such as "stearic acid/stearate salts from their tablets (especially magnesium stearate). See column 3, lines 33-35.

Makooi-Morehead et al disclose a compressed tablet or capsule comprising efavirenz, and one or more disintegrants that enhance the the dissolution rate of efavirenz in the gastrointestinal tract. The tablet requires the presence of a

lubricant, see item (f) in the list of ingredients in column 5, lines 40-50. Also, efavirenz is not in a salt form.

Motivation for combining references cannot be found where the proposed modification would render the prior art unsatisfactory for its intended purpose. MPEP § 2142, *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

Since Elger et al specifically excluded lubricants of the type required by Makooi-Morehead et al from their tablets, the use of Makooi-Morehead et al to modify the Elger et al tablet would result in the rendering of Elger et al unsatisfactory for its intended purpose. In this regard, the Examiner's attention is directed to Elger et al, column 5, lines 5 through column 7, line 15 where Comparative Examples A through C are described. In each of the Examples, tablets that contained lubricants exhibited various problems such as poor crushing strength, sticking problems on compression, unacceptable disintegration rates and discoloring. The claimed tablets contain a lubricant; however, by using Applicants' specific combination of ingredients, none of the problems disclosed by Elger et al are experienced with Applicants' tablet composition.

CLORPRES® PACKAGE INSERT

IN VIEW OF U.S. PATENT 6 238 695 (Makooi-Morehead et al)

CLORPRES® is a combination of clonidine hydrochloride and chlorthalidone (a diuretic) that produces a more pronounced antihypertensive response than occurs after either clonidine hydrochloride or chlorthalidine alone. The inactive ingredients of CLORPRES® tablets are:

ammonium chloride
colloidal silicon dioxide
croscarmellose sodium (Type A)
magnesium stearate
microcrystalline cellulose
sodium lauryl sulfate and

D&C yellow #10

None of these ingredients are polymeric binders, a required ingredient of the claimed tablet composition. Also, the relative amounts of the various ingredients are not disclosed in the CLORPRES® package insert.

There is no motivation to combine the CLORPRES® and Makooi-Morehead et al references because there is nothing in either reference that teaches or suggests such combination. The reason that the Examiner gives for combining the reference is that:

> "Nevertheless, it would have been obvious to one of ordinary skill in the art at the time of invention to employ lactose and colloidal silicone dioxide in suitable amounts within the compositions of Elger, or the formulation of Clorpres, and further optimize all concentrations in a tablet dosage form, because as taught by Makooi-Morehead, the ordinary artisan would have had a reasonable expectation of success in improving the rate of dissolution of a insoluble drug and subsequently its extent of absorption in GI track."

Makooi-Morehead et al does not either disclose or suggest that lactose and/or colloidal silicone dioxide improve the rate of dissolution. They specifically teach that the disintegrant or superdisintegrant is the ingredient that enhances the rate of dissolution of efavirenz (column 1, lines 14-20 and column 2, line 64 through column 3). There would be no motivation for one skilled in the art to add superdisintegrant to the Clorpres® tablet to enhance the dissolution rate of the active ingredients because the Clorpres® tablet already contains a superdisintegrant, namely croscarmellose sodium. Also, there would be no motivation to eliminate either one of the active ingredients since by doing so, the synergistic effect of the combination would be destroyed.

Even if combined, the Clorpres® package insert and Makooi-Morehead et al patent would still not establish a prima facie case of obviousness because neither reference discloses a tablet that contains a polymeric binder as that term is used

by Applicants. As pointed out above, none of the inactive ingredients contained in the Clorpres® tablet are polymeric binders. In making the rejection under 35 USC 103, the Examiner would modify the Clorpres® tablet by adding coloidal silicone dioxide and lactose to it. Colloidal silicone dioxide is considered by Makooi-Morehead et al to be a glidant and not a polymeric binder (see column 3, lines 29-32). Furthermore, colloidal silicone dioxide can be a separate ingredient in the claimed tablet composition, but it is not necessary to prepare the claimed tablet composition (see page 5 of Applicants' specification, lines 13-19). Finally, the Clorpres® tablet already contains colloidal silicone dioxide.

Lactose can also be a separate ingredient of the claimed tablet composition but its presence is also not absolutely necessary (see page 5, lines 5-12 of Applicants' specification). Since it optionally can be present as a separate ingredient in the claimed tablet composition, it would be clear to one skilled in the art that lactose is not included in Applicants' definition of a polymeric binder. The polymeric binder is a required ingredient of the claimed tablet composition.

In addition to not being a polymeric binder, as that term is used by the Applicants, lactose does not fit the generally accepted definition of a tablet binder, let alone a polymeric tablet binder. In the current common state of the art, lactose, which was disclosed by Makooi-Morehead et al, column 3, lines 22-23, to be a binder is more often considered to function primarily as a diluent, since it merely provides a limited degree of table bond. See The Merck Index, 11th (1989), paragraph 5221 and Handbook of Pharmaceutical Drug Excipients, Third Edition, page 276, copies of which are enclosed as Enclosures 1 and 2, respectively.

Since there is no motivation for combining the Clorpres® and Makooi-Morehead et al reference and their combination does not teach or suggest all of the limitations of claim 68, the

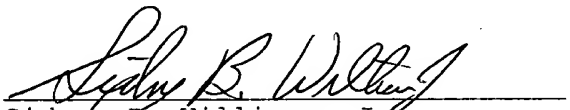
Examiner has not met the criteria for establishing a prima facie case of obviousness.

Specifically, the combination of the Clorpres® reference and Makooi-Morehead et al reference neither teach the use of a polymeric binder or the specific amounts of the ingredients recited in claim 1.

Since the dependent claims contain all of the limitations of claim 68, they are patentable over the combination of Elger et al and Makooi-Morehead et al and the combination of the Clorpres® reference for the same reason that claim 68 is patentable over the combination and because of the additional limitations contained in them.

In view of the above amendment and arguments, withdrawal of the rejections and expeditious passage of this application is respectfully solicited.

Respectfully submitted,



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Encl: The Merck Index, 11th Edition, 1989, page 843, paragraph 5221
Handbook of Pharmaceutical Drug Excipients, Third Edition, page 276
Postal Card

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ENCLOSURE 1

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

ELEVENTH EDITION

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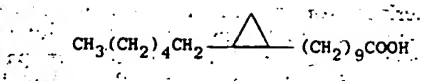
1989

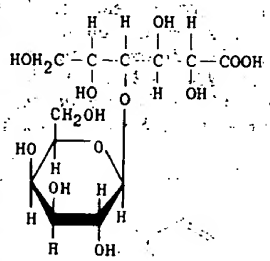


Crystals from acetone, mp 27.8-28.8°. Soluble in acetone, petr ether.

Methyl ester, $C_{20}H_{38}O_2$, liq, bp_3 187-187.5°. Soluble in many fat solvents.

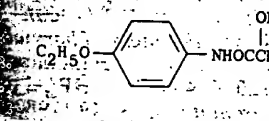
Amide, $C_{19}H_{37}NO$, *lactobacillamide.* Crystals, mp 79.4-81.5°. Soluble in dimethylformamide.

5219. Lactobionic Acid. *4-O-β-D-Galactopyranosyl-D-gluconic acid; 4-(β-D-galactosido)-D-gluconic acid.* $C_{12}H_{22}O_{12}$, mol wt 358.30. C 40.22%, H 6.19%, O 53.59%. Obtained by oxidation of lactose: Fischer, Meyer, *Ber.* **22,** 362 (1889); Ruff, Ollendorff, *ibid.* **33,** 1806 (1900); Isbell, *J. Res. NBS* **11,** 713 (1933); Margariello, U.S. pat. **2,746,916** (1956 to Nat. Dairy Res. Labs.); Eddy, *Nature* **181,** 904 (1958); Nishizuka *et al., J. Biol. Chem.* **235,** PC13 (1960). Manuf from lactose: Y. Sato *et al.,* Ger. pat. **2,038,230** (1971 to Hayashibara Co.), *C.A.* **74,** 142296c (1971). Crystal structure of calcium salt: W. J. Cook, C. E. Bugg, *Acta Crystallogr.* **B29,** 215 (1973). NMR studies: T. Taga *et al., Bull. Chem. Soc. Japan* **51,** 2278 (1978). For therapeutic use *see* Erythromycin Lactobionate.



Syrup. Freely sol in water, slightly sol in methanol, ethanol, glacial acetic acid. Dehydration by distillation with toluene yields *lactobionic δ-lactone,* $C_{12}H_{20}O_{11}$, non-deliquescent crystals, dec 195-196°. Shows mutarotation. $[\alpha]_D^{20}$ +38.6° initial (c = 8.8) → $[\alpha]_D^{20}$ +22.6° final (240 minutes). Calcium salt, $C_{24}H_{42}CaO_{24}$, *calcium lactobionate.* Pentahydrate, hairlike needles in brushlike groups. When anhydr, slender needles from small amts of anhydr ethanol. $[\alpha]_D^{20}$ +23.7° (c = 6.28). n_D^{20} 1.4583 (concd syrup just before crystallization). Freely sol in water.

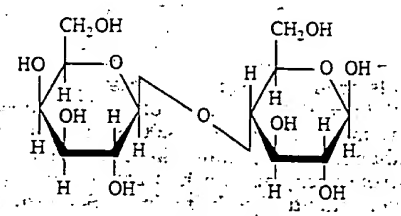
5220. *p*-Lactophenetide. *N-(4-Ethoxyphenyl)-2-hydroxypropanamide; p-lactophenetidide;* lactyl-*p*-phenetidin-*N*-(4-ethoxyphenyl)lactamide; Fenolactine; Lactophenin; Lactophenine. $C_{11}H_{15}NO_3$, mol wt 209.24. C 63.14%, H 7.24%, N 6.69%, O 22.94%. Prepn: Shapiro *et al., J. Am. Chem. Soc.* **81,** 6322 (1959).



Slightly bitter crystals from ethyl acetate + hexane, mp 118°. One gram dissolves in 330 ml cold, 55 ml boiling 95% alcohol; slightly sol in ether, petr ether.

THERAP CAT: Analgesic, antipyretic.

5221. Lactose. *4-O-β-D-Galactopyranosyl-D-glucose; 4-(β-D-galactosido)-D-glucose;* milk sugar. $C_{12}H_{22}O_{11}$, mol wt 342.30. C 42.10%, H 6.48%, O 51.42%. Present in milk of mammals: human 6.7%; cow's 4.5%. Milk at body temp contains lactose as an equilibrium mixture of 2 parts of α- and 3 parts of β-lactose. By-product of the cheese industry produced from whey: Davis, *Can. Dairy and Ice Cream J.* **19,** 52 (1940); *Milk Trade Gaz.* **12,** 4 (1941); F. Ullmann, *Encyklopädie der Technischen Chemie,* **VII,** 579 (1931). Structure and configuration: Zemplén, *Ber.* **59,** 1254 (1926); Levene, Sobotka, *J. Biol. Chem.* **71,** 471 (1927); Levene, Wintersteiner, *ibid.* **75,** 315 (1927); Haworth, *J. Chem. Soc.* **1927,** 544; Hudson, *J. Am. Chem. Soc.* **52,** 1689 (1930); Hassid, Ballou in *The Carbohydrates,* W. Pigman, Ed., (Academic Press, New York, 1957) p 495. Haskins *et al., J. Am. Chem. Soc.* **64,** 1852 (1942). *Reviews:* Whittier, *Chem. Rev.* **2,** 85-125 (1926); *J. Dairy Sci.* **27,** 505-537 (1944); Weisberg, *ibid.* **37,** 1106-1115 (1954); L. A. W. Thelwall, *Dev. Food Carbohyd.* **2,** 275-326 (1980).



α-Lactose monohydrate, is the usual milk sugar and the lactose of pharmacy. Monoclinic sphenoidal crystals from water. Faintly sweet taste. Stable in air, but readily absorbs odors. d^{20} 1.53. Becomes anhydrous at 120°. mp 201-202° (rapid heating). Shows mutarotation. $[\alpha]_D^{20}$ +92.6° → +83.5° (10 min.) → +69° (50 min) → +52.3° (22 hrs, c = 4.5). The final value is obtained instantly in the presence of a trace of NH_3. U.S.P. requires +52.2° to +52.5° (c = 10). One gram dissolves in 5 ml water, in 2.6 ml boiling water; very slightly sol in alcohol. Insol in chloroform, ether. Ka at 16.5° = 6.0×10^{-13}. d_4^{20} of aq solns calcd for the monohydrate: 5.2% = 1.018; 10.2% = 1.038; 20.0% = 1.078; 30.2% = 1.123; 50.9% = 1.226; 60.8% = 1.281; 69.1% = 1.330.

β-Lactose, $C_{12}H_{22}O_{11}$. Obtained by crystallizing concd solns of α-lactose above 93.5°. Somewhat sweeter than the α-form. $[\alpha]_D^{25}$ +34° (3 min) → +39° (6 min) → +46° (1 hr) → +52.3° (22 hrs). One gram dissolves in 2.2 ml water at 15°, in 1.1 ml boiling water. After a few days crystals of the less sol α-monohydrate appear from satd solns.

On hydrolysis with 2% H_2SO_4 or with emulsin lactose yields 1 mol D-glucose and 1 mol D-galactose. Reduces Fehling's soln.

USE: Both forms of lactose are employed, with the α-form predominating: as a nutrient in preparing modified milk and food for infants and convalescents (Whittier, "Lactose and Its Utilization," *loc. cit;* review with 327 ref). In baking mixtures. Pharmaceutic aid (tablet and capsule diluent). To produce lactic acid fermentation in ensilage and food products. As chromatographic adsorbent in analytical chemistry. In culture media. For many other uses see the comprehensive review by Weisberg "Recent Progress in the Manufacture and Use of Lactose," *loc. cit.*

THERAP CAT (VET): Added to cow's milk for feeding orphan foals.

5222. Lactucarium—"French". Thridace. Inspissated juice of *Lactuca sativa* L., var. *capitata* L., *Compositae. Constit.* Lactucin, hyoscyamine, mannite. Brown pieces or powder, bitter taste, opium-like odor. Partly sol in water, alcohol, ether.

5223. Lactucarium—"German". "Lettuce opium". Dried milk-juice of *Lactuca virosa* L., *Compositae* (wild lettuce). *Constit.* About 0.2% lactucin; about 50% lactucerol; hyoscyamine, lactucic acid, caoutchouc, volatile oil, mannite.

Brown powder or irregular pieces; wax-like when cut; bitter taste. Partly sol in water, alcohol, ether. *Keep dry.*

THERAP CAT: Sedative.

5224. Lactucin. *3,3a,4,5,9a,9b-Hexahydro-4-hydroxy-9-(hydroxymethyl)-6-methyl-3-methyleneazuleno[4,5-b]furan-2,7-dione.* $C_{15}H_{16}O_5$, mol wt 276.30. C 65.21%, H 5.84%, O 28.95%. From various *Lactuca* spp and *Cichorium intybus* L., *Compositae.* Isoln: Schenck, Graf, *Arch. Pharm.* **274,** 537 (1936); **275,** 36 (1937); Schenck *et al., ibid.* **294,** 17 (1961). Purification: Späth *et al., Monatsh.* **82,** 114 (1951). Structure: Dolejs *et al., Coll. Czech. Chem. Commun.* **23,** 2195 (1958); Barton, Narayanan, *J. Chem. Soc.* **1958,** 963; Michl, Högenauer, *Monatsh.* **89,** 317 (1958). Revised stereochemistry: Bachelor, Itô, *Can. J. Chem.* **51,** 3626 (1973).

ENCLOSURE 2

Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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Lactose

1. Nonproprietary Names

BP: Lactose monohydrate
JP: Lactose
PhEur: Lactosum
USP: Lactose monohydrate

Note that the JP and USP also contain a monograph for anhydrous lactose, *see* Sections 9 and 19.

2. Synonyms

Fast-Flo; 4-(β-D-galactosido)-D-glucose; *Lactochem*; *Microtose*; milk sugar; *Pharmatose*; saccharum lactis; *Tablettose*; *Zeparox*.

3. Chemical Name and CAS Registry Number

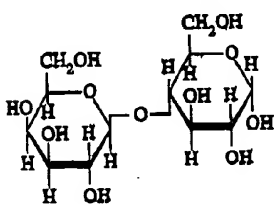
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous [63-42-3]

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5]

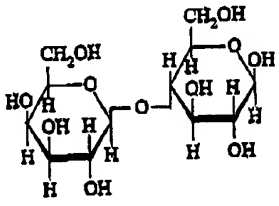
4. Empirical Formula / Molecular Weight

Empirical Formula	Molecular Weight
$C_{12}H_{22}O_{11}$	342.30 (anhydrous)
$C_{12}H_{22}O_{11}.H_2O$	360.31 (monohydrate)

5. Structural Formula



α - lactose



β - lactose

6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets, capsules, and to a more limited extent in lyophilized products and infant feed formulas.[1-15]

Various lactose grades are commercially available which have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application, e.g., the particle size range selected for capsules is often dependent upon the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include as a carrier/diluent for inhalation products and in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid caking. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

The method for obtaining lactose from milk was patented in 1937.[16] The process for making spray-dried lactose for use as direct-compression excipient was patented in 1958.[17] Thereafter it has been used as the standard of comparison for all modern direct-compression excipients. It is possibly the most studied excipient and the extent of the literature published yearly is too broad to be included here.[18,19] Today, many other lactose grades are commercially available, including anhydrous α-lactose, α-lactose monohydrate, and to a minor extent, anhydrous β-lactose.

Generally, the grade of lactose chosen is dependent on the type of dosage form being developed. Direct-compression grades are often used to carry small quantities of drug and this permits tablets to be made without granulating.

Direct-compression grades of lactose are more fluid and more compressible than crystalline or powdered lactose and are generally composed of spray-dried lactoses which contain specially prepared pure α-lactose monohydrate along with a small amount of amorphous lactose. The amorphous lactose improves the compression force/hardness profile of the lactose. Other specially produced direct-compression grades of lactose do not contain amorphous material but may contain glassy or vitreous areas which impart improved compressibility. Direct-compression grades of lactose may also be combined with microcrystalline cellulose or starch, and usually require a tablet lubricant such as 0.5% w/w magnesium stearate. The use of direct-compression grades of lactose results in tablets of higher breaking strength than standard lactose. Concentrations of lactose generally used in these formulations are from 65-85%. Lower amounts of spray-dried lactose can be used if additional direct-compression material such as pregelatinized starch is substituted.

8. Description

White to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 15% as sweet as sucrose, while β-lactose is sweeter than the α-form.

Several different forms of lactose are commercially available: anhydrous α-lactose, α-lactose monohydrate, and to a lesser extent, anhydrous β-lactose which typically contains 70% anhydrous β-lactose and 30% anhydrous α-lactose, although grades containing a greater quantity of anhydrous β-lactose are also available, e.g., *Pharmatose DCL 21* (DMV International). α-Lactose may also contain a small quantity of the β-form.

SEM: 1
Excipient: Lactose monohydrate (*Lactose D30*)
Manufacturer: Meggle GmbH